Genome-wide and abdominal MRI-imaging data provides evidence that a genetically determined favourable adiposity phenotype is characterized by lower ectopic liver fat and lower risk of type 2 diabetes, heart disease and hypertension.

Yingjie Ji*[1], Andrianos M. Yiorkas*[2,3], Francesca Frau*[4], Dennis Mook-Kanamori*[5,6], Harald Staiger*[7,8,9], E. Louise Thomas[10], Naeimeh Atabaki-Pasdar[11], Archie Campbell[12], Jessica Tyrrell[1], Samuel E. Jones[1], Robin N. Beaumont[1], Andrew R. Wood[1], Marcus A. Tuke[1], Katherine S. Ruth[1], Anubha Mahajan[13], Anna Murray[1], Rachel M. Freathy[1], Michael N. Weedon[1], Andrew T. Hattersley[14], Caroline Hayward[15], Jürgen Machann[7,8], Hans-Ulrich Häring[7,8,16], Paul Franks[11,17,18], Renée de Mutsert[5], Ewan Pearson[19], Norbert Stefan*[7,8,16], Timothy M. Frayling*[1], Karla V. Allebrandt*[4], Jimmy D. Bell*[10], Alexandra I. Blakemore*[2,3], Hanieh Yaghootkar*[#1]

* Contributed equally

[#] Corresponding author

1- Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, RILD Level 3, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

2- Section of Investigative Medicine, Imperial College London, London W12 0NN, UK

3- Department of Life Sciences, Brunel University London, Uxbridge UB8 3PH, UK

4- Translational Medicine and Early Development, TMED Translational Informatics, Sanofi, Frankfurt am Main, Germany

5- Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

6- Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

7- Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Otfried Müller Strasse 10, 72076 Tübingen, Germany

8- German Center for Diabetes Research (DZD), Otfried-Müller-Strasse 10, 72076 Tübingen, Germany

9- Institute of Pharmaceutical Sciences, Department of Pharmacy and Biochemistry, Eberhard Karls University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany

10- Research Centre for Optimal Health, School of Life Sciences, University of Westminster, London, UK

11- Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund

University, Skåne University Hospital Malmö, SE-21741, Malmö, Sweden.

12- Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

13- Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK.

14- Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter EX2 5DW, UK

15- Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

16- Department of Internal Medicine IV, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, Eberhard Karls University Tübingen, Otfried-Müller-Strase 10, 72076 Tübingen, Germany

17- Department of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden.

18- Department of Nutrition, Harvard School of Public Health, Boston, MA, USA.

19- Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital, Dundee, UK

Corresponding author: Hanieh Yaghootkar

University of Exeter Medical School, RILD building Level 3, Royal Devon & Exeter

Hospital, Barrack Road, Exeter, EX2 5DW

E-mail: h.yaghootkar@exeter.ac.uk

Work count: 4,200

Number of tables and figures: 5

Abstract (200 words)

Recent genetic studies have identified alleles associated with opposite effects on adiposity and risk of type 2 diabetes. We aimed to identify more of these variants and test the hypothesis that such "favourable adiposity" alleles are associated with higher subcutaneous fat and lower ectopic fat. We combined magnetic resonance imaging (MRI) data with genome-wide association studies (GWAS) of body fat % and metabolic traits. We report 14 alleles, including 7 newly characterized alleles, associated with higher adiposity, but a favourable metabolic profile. Consistent with previous studies, individuals carrying more "favourable adiposity" alleles had higher body fat % and higher BMI, but lower risk of type 2 diabetes, heart disease and hypertension. These individuals also had higher subcutaneous fat, but lower liver fat and lower visceral-to-subcutaneous adipose tissue ratio. Individual alleles associated with higher body fat % but lower liver fat and lower risk of type 2 diabetes included those in *PPARG, GRB14* and *IRS1*, whilst the allele in *ANKRD55* was paradoxically associated with higher visceral fat but lower risk of type 2 diabetes. Most identified "favourable adiposity" alleles are associated with higher subcutaneous and lower liver fat, a mechanism consistent with the beneficial effects of storing excess triglyceride in metabolically low risk depots.

Introduction

There are many overweight or obese individuals who do not carry the expected metabolic disease risks associated with higher BMI (1; 2) while some lean or normal weight individuals develop diseases like type 2 diabetes(3-5). We(6; 7) and others(8-10) have previously shown that genetic variation is likely to contribute to these differences by increasing adiposity but lowering the risk of type 2 diabetes. We labelled these variants "favourable adiposity" since the alleles associated with higher BMI are associated with a favourable metabolic profile and lower risk of type 2 diabetes. The alternative alleles of the same variants could be characterized as "unfavorable lack of adiposity" or "limited adipose tissue storage capacity". The identification of these variants differed by study. One study started with a genome-wide association study (GWAS) of body fat % in 76,150 individuals and showed that a common allele near the *IRS1* gene was associated with higher adiposity but lower insulin resistance and risk of disease(8). The remaining studies were limited to genetic variants associated with fasting insulin levels at genome-wide levels of statistical confidence and used a combination of data and approaches to identify genetic scores of between 10 and 53 variants that collectively were associated with opposite effects on BMI and risk of type 2 diabetes(6; 7; 9; 10).

More detailed characterization of these alleles revealed several insights. First, the alleles associated with higher BMI but lower risk of type 2 diabetes were associated with a lower risk of hypertension and heart disease as well as type 2 diabetes(6; 7; 9). Second, most of the alleles associated with higher insulin sensitivity, as identified by GWAS of fasting insulin levels, were associated with higher BMI or a redistribution of fat into the lower body, as estimated by waist-to-hip ratio(6; 7; 9; 10). Third, these

alleles were associated with more refined measures of adipose tissue distribution: the alleles associated with higher BMI but lower risk of disease were also associated with higher adiposity in the lower body (gynoid area and legs) as measured by DEXA(9).

The association of "favourable adiposity" alleles with higher peripheral adiposity in the previous studies proposed that a likely explanation for the mechanism is altered adipose tissue storage capacity(6; 7; 9; 10) consistent with the "adipose tissue expandability" hypothesis(11). To have a clear understanding about the underlying mechanisms associated with "favourable adiposity" in the context of the "adipose tissue expandability" hypothesis, we need to study whether "favourable adiposity" alleles are specifically associated with lower levels of ectopic fat. Furthermore, since men and women have different body fat distribution regulated by sex steroids(12), the study of underlying mechanisms separately in men and women may help elucidate the biology of the cardio-metabolic diseases.

The aim of this study was to identify additional alleles associated with "favourable adiposity" and to combine genetic and MRI data to understand more about the underlying mechanisms. In contrast to most previous studies, that focused on variants associated with surrogate measures of insulin resistance (fasting insulin), we started with variants associated with altered body fat %. We describe an approach that led to the characterization of 14 alleles collectively associated with higher body fat % but lower risk of type 2 diabetes, hypertension and heart disease. We showed that these alleles are associated with lower ectopic fat in the liver, based on MRI data.

Method

UK Biobank study: UK Biobank recruited over 500,000 individuals aged 37-73 years (99.5% were between 40 and 69 years) between 2006-2010 from across the UK (**supplementary table 1**). The study has been described in more detail elsewhere(13).

UK Biobank genetic data: SNP genotypes underwent extensive central quality control (http://biobank.ctsu.ox.ac.uk). We based our study on 451,099 individuals of white European descent as defined by Principal Components Analysis (PCA). Briefly, principal components were generated in the 1000 Genomes Cohort using high-confidence SNPs to obtain their individual loadings. These loadings were then used to project all of the UK Biobank samples into the same principal component space and individuals were clustered using principal components 1-4. We removed 7 participants who withdrew from the study, and 348 individuals whose self-reported sex did not match their genetic sex based on relative intensities of X and Y chromosome SNP probe intensity.

Measures of disease and disease related traits in UK Biobank: We used 3 cardio-metabolic diseases: type 2 diabetes, hypertension (also represented by continuous measures of systolic and diastolic blood pressure) and heart disease – all using baseline data and following similar definitions to those used in previous GWASs (**supplementary table 1**).

We defined type 2 diabetes cases using baseline data if 3 criteria were present: i) reports of diabetes at the interview, ii) at least one year gap from diagnosis without requiring insulin, iii) reported age at diagnosis over the age of 35 years to limit the numbers of individuals with slow-progressing autoimmune diabetes or monogenic forms. Individuals not reporting an age of diagnosis were excluded. We also excluded

individuals diagnosed with diabetes within the year prior to the baseline study visit as we were unable to determine whether they were using insulin within the first year. Controls were individuals not fulfilling these criteria.

We defined subjects as hypertensive if systolic blood pressure was >140 mmHg, or a diastolic blood pressure was >90 mmHg, or blood pressure medication was reported. Controls were individuals not fulfilling these criteria. For the analysis of systolic and diastolic blood pressure, we corrected blood pressure measures in people on antihypertensive drugs by adding 15 mmHg to systolic and 10 mmHg to diastolic blood pressure.

We defined heart disease cases if individuals reported angina and/or a heart attack at the interview stage. We defined controls as individuals without these conditions.

Identification of genetic variants associated with "favorable adiposity"

We designed a study in three steps to identify genetic variants associated with "favourable adiposity" (**supplementary figure 1**).

First, genetic variants associated with adiposity. We used Bio-impedance measures of body fat % measured by the Tanita BC418MA body composition analyser as measure of adiposity (N = 442,278 individuals from UK Biobank). We used a linear mixed model implemented in BOLT-LMM to account for population structure and relatedness(14). We used age, sex, genotyping platform, study centre and the first 5 principal components as covariates in the model.

Second, genetic variants associated with a multivariate metabolic outcome: We used summary statistics from published GWASs (not including UKBiobank) of metabolic biomarkers including body fat % (N = 120,000)(15), HDL-C (99,900)(16),

adiponectin (29,400)(17), sex hormone binding globulin (SHBG, 21,800)(18), triglycerides (96,600)(16), fasting insulin (51,800)(19), and alanine transaminase (55,500)(20). We used these biomarkers to be consistent with our previous approach(7). These biomarkers are used to discriminate monogenic disorders of fat storage (lipodystrophy) from other monogenic conditions where insulin sensitivity and adiposity are affected(7; 21; 22).

Within each GWAS, we standardized the effect sizes to correct for the differences in sample size and the various traits measurement unit across different GWAS:

$$beta_{standardized} = \frac{beta}{se * \sqrt{n}}$$

We used metaCCA(23) to run a multivariate GWAS. The phenotype-phenotype correlation matrix (Σ^YY=cov(Y, Y)) was built according to the Pearson correlation between any pairs of traits across genome-wide genetic variants. Genotype-genotype correlation matrix (Σ^XX=cov(X, X)) was computed using reference database from 1000 Genomes. The canonical correlation analysis in metaCCA finds the maximal correlation coefficient R_metaCCA between genetic variants and linear combination of phenotypes based on phenotype-phenotype correlation matrix. We defined genetic variants associated with a multivariate metabolic outcome if metaCCA $p < 5x10^{-8}$.

Third, genetic variants associated with "favourable adiposity". We selected genetic variants associated with both adiposity (step 1) and a multivariate metabolic outcome (step 2) at $p < 5x10^{-8}$ and used a hierarchical clustering approach to narrow down the list to ones showing a pattern of "favourable adiposity". We calculated the frequency of times the variants were in the same cluster to identify "favourable adiposity" cluster using the "pvclust" package in R as shown before(7).

Genetic score analysis

We constructed the genetic score of "favorable adiposity" variants as the number of "favorable adiposity" alleles carried by each individual (un-weighted). We used age, sex, genotyping platform, study center and the first 5 ancestry principal components as covariates in the model.

Additional studies for replication of the non-imaging findings

To provide further evidence for the role of "favorable adiposity" alleles, we used 5 cohorts that were not part of the published GWASs used in our discovery stage (**supplementary table 1**): NEO study (The Netherlands Epidemiology of Obesity; 6,671 individuals of white European descent collected from the greater area of Leiden in the West of the Netherlands(24)), EXTEND (Exeter 10,000; 7,340 individuals of white European descent collected from South West England), GS:SFHS (Generation Scotland: Scottish Family Health Study; 20,000 individuals of white European descent collected from Scotland(25)), TÜF (Tübingen Family Study for Type 2 Diabetes; 2,679 individuals of white European descent collected from Southern Germany(26)), and IMI-DIRECT (Diabetes Research on Patient Stratification; 3,029 Caucasian pre-diabetic and Type 2 Diabetes subjects recruited by clinical centers located across Europe(27)).

To further provide evidence for the role of "favorable adiposity" alleles in risk of cardiometabolic diseases, we used published GWAS studies of type 2 diabetes(28), heart disease(29) and blood pressure(30).

Studies contributed to imaging findings (liver fat, visceral fat and subcutaneous fat):

UK Biobank: We used 5,045 individuals who had available data obtained through UK Biobank Access Application number 9914 and 6569. Participants were MRI scanned as previously described(31). Briefly, a single transverse slice located at the liver was acquired from each subject using multi-echo spoiled-gradient-echo acquisition and analysed as previously described(32). Assessment of abdominal subcutaneous and visceral fat was described previously(33).

NEO: Abdominal subcutaneous and visceral fat was assessed in 2,236 participants using MRI and were quantified by a turbo spin echo imaging protocol. At the level of the 5th lumbar vertebra 3 transverse images each with a slice thickness of 10 mm were obtained during a breath-hold. Proton (^{1}H)-MRS of the liver was used to assess hepatic triglyceride content (N = 1,821)(24).

TÜF: The TÜF study contributed subcutaneous and visceral adipose tissue measurements from 833 and 906 genotyped individuals, respectively, who underwent whole body magnetic resonance tomography. The two fat depots were quantified by an axial T1-weighed fast spin echo technique with a 1.5 T whole-body imager (Magnetom Sonata, Siemens Healthcare), as previously described(26). Liver fat measurements were available from 911 genotyped individuals who underwent localized ^{1}H magnetic resonance spectroscopy, as described(26).

IMI-DIRECT: The IMI-DIRECT consortium is a collaboration among investigators from a range of European academic institutions and pharmaceutical companies. Liver fat was assessed on 1,457 subjects using a multi-echo acquisition as previously described(34). Briefly, the liver was identified from a scout abdominal image and axial images were performed during suspended respiration, which were used to position a single slice multi-echo sequence through the liver.

Published GWAS: We used published genome-wide association study of subcutaneous and visceral fat distribution as measured by CT scan or MRI(35).

Results

We identified 14 alleles associated with "favourable adiposity"

Using a 3-step approach, we characterized 14 genetic variants associated with "favourable adiposity". Of these variants, seven were previously known to be associated with a "favourable adiposity" phenotype - those in/near *PPARG, LYPLAL1, GRB14, IRS1, PEPD, FAM13A and ANKRD55*, five were known to be associated with a relevant trait, but not confirmed as having a "favourable adiposity" phenotype, (those in/near *TRIB1, KLF14/MKLN1, DNAH10, VEGFA/C6orf223* and *AEBP2/PDE3A*) and two were entirely novel (those in/near *MAFF* and *CITED2*) (**supplementary table 2**). Twelve of the 14 variants had not previously been associated with body fat % at genome-wide levels of statistical confidence.

In the first step (**supplementary figure 1**), we performed a GWAS of body fat % in 442,278 individuals in the UK Biobank. We identified 620 variants at $p<5x10^{-8}$. In the second step, we used published GWAS statistics from 7 circulating biomarkers of metabolic health and identified 33 of these 620 variants as associated with a multivariable metabolic phenotype. This approach identifies alleles associated with metabolic traits after accounting for the phenotypic correlation between higher adiposity and these metabolic traits (**supplementary table 3 & 4, supplementary figure 2**). For example, this approach has more power to detect alleles paradoxically associated with higher adiposity but a favourable metabolic profile, because the model accounts for the population level correlation between higher adiposity and an adverse metabolic profile. The resulting 33 alleles also included some alleles associated very strongly with higher BMI and adverse metabolic profile, such as the allele in the *FTO* gene, most likely because adjusting for body fat % in the model does not fully account

for the adverse metabolic effects of lifelong higher adiposity. We therefore undertook a third step where we further refined the phenotypic characteristics of these variants by performing a clustering analysis. This approach led to the clustering of 14 alleles associated with "favourable adiposity" as defined by association with higher body fat %, HDL-C, SHBG and adiponectin levels, and lower triglycerides, alanine transaminase and fasting insulin levels (**supplementary figure 3**). We validated the effect of the 14 "favourable adiposity" alleles together in a genetic score on levels of metabolic biomarkers using 5 independent studies: NEO, EXTEND, GenScotland, TÜF and IMI-DIRECT (**supplementary table 5**).

A genetic score of "favourable adiposity" alleles was associated with lower risk of cardiometabolic disease outcomes.

Carrying additional "favourable adiposity" alleles was associated with higher body fat % and higher BMI but lower risk of type 2 diabetes, hypertension and heart disease (**table 1**). For example, the 10% of people carrying the most "favourable adiposity" alleles had approximately 1.04% higher body fat % (95%CI [0.95,1.13], $p=6x10^{-115}$) and 0.4 kg/m^2 higher BMI ([0.32,0.45], $3x10^{-29}$) but 0.66 OR lower risk of type 2 diabetes ([0.61,0.72], $7x10^{-23}$), 0.87 lower risk of hypertension ([0.84,0.90], $1x10^{-19}$) and 0.84 OR lower risk of heart disease ([0.80,0.89], $6x10^{-10}$) compared to the 10% of people carrying the fewest "favourable adiposity" alleles (data from UK Biobank) (**figure 1**). These effects were similar in men and women and when we removed the seven known "favourable adiposity" variants from the analysis (**table 1**). These associations were similar when using data from published GWASs (**supplementary table 6)**. For each of the 14 individual variants, the body fat % increasing allele was associated with at least one of lower risk of type 2 diabetes, lower risk of heart disease

or lower diastolic or systolic blood pressure in UK Biobank except the variant at the *AEBP2* locus (**supplementary figure 4**). In published GWAS data the exceptions were the variants at the *AEBP2* and *MAFF* loci (**supplementary table 6)**.

Individual "favourable adiposity" alleles were associated with heterogeneous effects on waist-to-hip ratio.

Five of the individual 14 variants were previously identified as associated with waist-to-hip ratio(36). Previous studies have pointed out that the disease-protective effect of these alleles is likely to be due to their association with redistribution of the extra fat into the lower body (defined by lower waist-to-hip ratio). We therefore examined the alleles' association with waist-to-hip ratio in more detail. Carrying more "favourable adiposity" alleles was associated with lower waist circumference ($p=3.7x10^{-5}$) but higher hip circumference ($2.3x10^{-109}$) in women. However, in men, carrying more "favourable adiposity" alleles was associated with higher waist circumference ($1.7x10^{-40}$), higher hip circumference ($1.8x10^{-53}$) and no effect on waist-to-hip ratio (**supplementary table 7)**. These associations were robust when limiting the variants to the 7 not previously identified as having a "favourable adiposity" phenotype (**supplementary table 7)**. The individual variants were associated with heterogeneous effects on waist-to-hip ratio. Most notably, for two variants, those in/near *PPARG* and *ANKRD55*, the "favourable adiposity" allele was not associated with lower waist-to-hip ratio in women, and for *ANKRD55*, it was associated with higher waist-to-hip ratio (**figure 2**).

"Favourable adiposity" alleles were associated with less liver fat and more abdominal subcutaneous fat.

We next investigated the associations between the "favourable adiposity" variants and MRI measures of subcutaneous, visceral and liver fat using data from 9,434 individuals and 4 studies – the first wave of UK Biobank imaging data (n=5,045), NEO (2,236), IMI-DIRECT (1,323) and TÜF (906). A fifth set of data did not include liver fat and came from a published meta-analysis of 13 studies with abdominal MRI or CT scans of 18,332 individuals(35).

The genetic score of "favourable adiposity" alleles was associated with lower visceral-to-subcutaneous adipose tissue ratio $p=2x10^{-14}$) in both men and women. This effect was driven by association with more subcutaneous fat ($p=2x10^{-14}$; **table 2, figure 3**). All 14 individual genetic variants were associated with higher subcutaneous adipose tissue, seven at $p<0.05$ (in/near *DNAH10, FAM13A, GRB14, KLF14, LYPLAL1, IRS1* and *PPARG*). Nine individual "favourable adiposity" alleles were associated with lower visceral-to-subcutaneous adipose tissue volume ratio, all at $p < 0.05$ (in/near *CITED2, DNAH10, FAM13A, KLF14, LYPLAL1, IRS1, PPARG, TRIB1* and *VEGFA*; **supplementary figure 4, supplementary table 8**). Paradoxically, the "favourable adiposity" alleles in/near *ANKRD55* and *PEPD* were associated with higher visceral-to-subcutaneous adipose tissue volume ratio (p=0.001 and 0.02, respectively).

The genetic score of "favourable adiposity" was associated with lower liver fat in women ($p=6.3x10^{-9}$) but was not associated with liver fat in men (p=0.8; **table 2, figure 3**). These effects were robust when limiting the variants to the 7 not previously identified as having a "favourable adiposity" phenotype (**table 2**). For 11 individual variants, the allele associated with higher subcutaneous fat was associated with lower liver fat, four with $p<0.05$ (in/near *CITED2, GRB14, PPARG* and *TRIB1* (**supplementary figure 4, supplementary table 8**).

Sensitivity analysis of liver fat.

We performed three sensitivity analyses to assess whether the effect of "favourable adiposity" alleles on lower liver fat was affected by menopause, inclusion of type 2 diabetes patients or alcohol consumption.

First, menopause leads to a redistribution of adipose tissue towards more central obesity and an android phenotype(37; 38). To study whether or not the association with liver fat in women was influenced by menopausal status, we divided women from the UK Biobank and TÜF studies into pre- and post-menopausal status. The association between "favourable adiposity" alleles and lower liver fat in pre-menopausal women was twice that (-0.258 % [-0.223,-0.293]; p=0.002; n=433) of post-menopausal women (-0.124 % [-0.106,-0.142]; p=0.002; n=2,356) but the difference was not statistically meaningful ($P_{difference}$=0.14; **supplementary table 9**).

Second, fatty liver disease is very common (>50%) in patients with type 2 diabetes(39). To check whether inclusion of people with type 2 diabetes had affected the association with liver fat, we ran the tests in UK Biobank individuals excluding people diagnosed with type 2 diabetes (n=222) from the analysis of liver fat. The association of "favourable adiposity" alleles with liver fat remained similar after exclusion of patients with type 2 diabetes in all, men and women (all $P_{difference}$>0.7; **supplementary table 10**).

Third, the most common cause of increased fat in the liver is alcohol consumption which is more prevalent in men(40; 41). To study whether or not the lack of association with liver fat in men was due to greater alcohol consumption, we assessed the effect of "favourable adiposity" alleles on liver fat in men defined as heavy, moderate and non-

drinkers based on self-report alcohol questionnaires. The “favourable adiposity” alleles were not associated with liver fat in any of the three groups (**supplementary table 11**).

Discussion

We characterized 14 genetic variants associated with "favourable adiposity". Our study adds to previous studies(6; 7; 9; 10) in several ways. First, we outlined a new approach which leads to the identification of more "favourable adiposity" variants. Second, we provide more clarity about which individual alleles are likely "favourable adiposity" alleles and how they affect metabolic traits and diseases. Third, we used MRI data which strongly suggests these variants have a collective effect on lower liver fat as well as higher subcutaneous fat but they have little detectable effect on visceral fat. Finally, we provide a template for detecting alleles with apparently paradoxical effects on adiposity and disease using a wide variety of publically accessible GWAS data. In addition, our results strengthen previous observations including the "favourable adiposity" effect is not driven by altered body shape in men detectable by waist-to-hip ratio (6).

Of the 14 variants detected, 12 had been associated with at least one metabolic trait, including fasting insulin (those in/near *LYPLAL1, GRB14, IRS1, FAM13A, ANKRD55* and *PEPD (42)*), lipid levels (those in/near *GRB14, IRS1, KLF14, TRIB1* and *DNAH10* (16)), adiponectin (those in/near *TRIB1, DNAH10* and *AEBP2*(17)) and alanine transaminase (*TRIB1*(20)). However, only two were known to be associated with body fat % (those in/near *GRB14* and *IRS1*(15)) at genome-wide levels of statistical confidence. Our data provides several insights about individual variants. First, the alleles at *PPARG, GRB14* and *IRS1* are associated with higher body fat % but lower liver fat and lower risk of type 2 diabetes. Second, the allele in *ANKRD55* is paradoxically associated with higher visceral fat but lower risk of type 2 diabetes. In agreement with this finding, this variant is in high linkage disequilibrium (R^2= 0.97)

with another variant (rs459193) found to associate with lower waist circumference, but higher 2-houre glucose levels(43). Third, the allele in *TRIB1* is associated with higher body fat %, lower visceral fat, lower liver fat and lower risk of heart disease and hypertension but it does not have any detectable effect on type 2 diabetes. Fourth, 4 variants we previously noted as favourable adiposity were not detected in this study. These variants (in or near *PDGFC, PEPD, RSPO3* and *TET2*) may alter body fat distribution or other aspects of body composition without altering overall body fat %, and hence were not detected at $p<5x10^{-8}$ in stage 1.

A key question is whether or not the "favourable adiposity" effect is entirely due to preferential storage of the excess adiposity in the lower body as proposed before(36; 44). We made two general observations. First, despite similar effects on higher body fat % and lower risk of disease in each sex, the protective effect in men was not characterized by preferentially more fat in the lower body, as estimated by waist-to-hip ratio, consistent with our previous observation(6). Second, the individual variants were associated with heterogeneous effects on waist-to-hip ratio even within women. For example the allele in/near *ANKRD55* was associated with "favourable adiposity" but higher waist-to-hip ratio in women.

Having established that the "favourable adiposity" effect is not driven by preferential storage of fat in the lower body, as estimated by waist-to-hip ratio, in men, we examined more detailed measures of fat redistribution using MRI data. The association with lower liver fat was only detected in women. Our sensitivity analyses did not find hormonal differences due to menopause, alcohol consumption or type 2 diabetes as possible explanations for sex differences. We would expect the "favourable adiposity" alleles to be associated with liver fat in non-drinkers or moderate drinkers if the alcohol intake in

men confounded the association. However, the analysis stratified by alcohol intake in men did not show any association. The lack of association with visceral fat suggests that these alleles were not protecting from disease due to lower visceral fat. This observation is consistent with some studies which showed lower ectopic fat accumulation in the liver may be more important than visceral fat in protection from risk of type 2 diabetes(45). A caveat to this conclusion is that we used a marker of liver fat, alanine transaminase, as one of the metabolic biomarkers to identify the variants, and therefore will be biased towards those that affect liver more than visceral fat.

Our approach provides a framework for identifying additional alleles with apparently paradoxical effects on adiposity and disease. A previous study(9) used a simple and effective approach by taking published GWAS data and selecting all variants associated with higher fasting insulin adjusted for BMI, lower HDL-C and higher triglycerides at $p<0.005$ for each of the three traits. However, this approach has limitations for two reasons, first it applies an arbitrary cut-off for the three traits, and second, it does not use information from other biomarkers. We combined GWASs of seven metabolic biomarkers and used a multivariate test that does not require individual trait associations to reach a certain statistical threshold. We showed that our method performs well, as it was able to identify the 7 variants previously known to be associated with "favourable adiposity" as well as 7 additional variants that we then validated in independent GWAS data. Furthermore, by including SHBG, adiponectin and ALT in the model, we had more power to detect "favourable adiposity" variants (**supplementary table 12**).

The identification of "favourable adiposity" alleles highlights genes that may be targets for novel insulin-sensitizing agents. The allele in *PPARG* provides an important proof

of principle because thiazolidinediones are PPAR-γ agonists and appear to lower glucose levels despite increasing the patient's weight by activating adipocyte differentiation, which redistributes fat away from liver towards an expanded subcutaneous depot(46; 47). The variants identified in our study do not identify which genes they are acting through; however, previous studies suggest some strong candidates. For example, *TRIB1* encodes a protein critical for adipose tissue maintenance and suppression of metabolic disorders(48). Mice lacking Trib1 show diminished adipose tissue mass and increased lipolysis even when on a normal diet(48). GWAS studies in humans have implicated *TRIB1* in lipid metabolism(16) and regulation of hepatic lipogenesis(20). Higher levels of VEGF-A in mice can facilitate healthy expansion of adipose tissue and protect from lipotoxicity and metabolic disease(49). *CITED2* is required for optimal PPARγ activation(50). *FAM13A* encodes a protein enriched in mature adipocytes and plays an important role in the insulin signaling cascade(51) by protecting IRS1 (insulin receptor substrate 1) from degradation(51). The proteins encoded by *IRS1* and *CCDC92* are associated with adipogenesis, lipid accumulation and adipocyte differentiation ability(9; 51). Functional studies suggest *DNAH10* is involved in adipocyte differentiation capacity(9). *KLF14* is a master regulator of gene expression in adipose tissue(52) associated with adipocyte cell size in humans(53). *MAP3K1* regulates expression of *IRS1*(54). *LYPLAL1*, as a triglyceride lipase, is over-expressed in subcutaneous adipocytes of obese people to maintain triglycerides metabolism(55). The regulation of Grb14 expression in adipose tissue may play a physiological role in insulin sensitivity(56). *AEBP2* regulates a gene encoding a fatty acid-binding protein.

Our study had a number of limitations. First, we used 7 metabolic biomarkers from published GWASs in our multivariate analysis. The sample size for each GWAS was

different: ranging from 21,800 individuals from GWAS of SHBG to 99,900 from the GWAS of lipids. These differences, caused by using GWAS meta-analysis data from different studies, will have limited our power, and led to less accurate estimates of the correlation between phenotypes compared to having the same sample size for all phenotypes. Second, the published GWASs of biomarkers were performed in men and women together rather than in a sex specific way. As men and women have different body fat distribution, it seems necessary to perform the discovery of "favourable adiposity" variants in men and women separately when data becomes available. Third, we used bio-impedance measures of body fat % as measure of adiposity in the discovery step. This measure of adiposity is an imprecise measure and is not as accurate in calculating body fat % in obese individuals or people with higher muscle mass(57). However, it's availability in 442,278 individuals meant it represented a powerful dataset from which to start(58). Fourth, individual variants had subtle effect sizes; all variants were associated with at least one disease, with the body fat % increasing allele associated with lower risk except the one at *AEBP2* locus; although this variant had a paradoxical effect on adiposity and metabolic biomarkers with significant association between body fat % increasing allele and higher adiponectin ($p= 4.76x10^{-8}$), higher HDL-C ($p=2.83x10^{-6}$) and lower triglycerides (p=0.003; **supplementary table 4**).

To yield a better understanding of how "favourable adiposity" protects against cardiometabolic disease, more studies in future are warranted. First, it will be important to test the association of "favourable adiposity" variants with pancreatic fat as a potential cause of β-cell dysfunction that will inform the associations with type 2 diabetes. Second, there are substantial ethnic differences in diabetes risk by BMI with South Asians having a much higher risk of type 2 diabetes for a given BMI compared to Europeans(59). Study of the genetics of "favourable adiposity" in different ethnic

groups may provide important insights into the mechanisms underpinning the significant ethnic differences in diabetes risk.

In summary, our study provides further genetic evidence that the balance of subcutaneous to ectopic liver fat is an important factor for type 2 diabetes, heart disease and hypertension. This finding is consistent with data from monogenic forms of lipodystrophy and the importance of an expandable subcutaneous adipose tissue as a protective disease mechanism and limited adipose storage capacity as a risk mechanism (based on the opposite alleles) as proposed in previous studies(60-62).

Acknowledgment

The authors thank University of Exeter Medical School. EXTEND data were provided by the Peninsula Research Bank, part of the NIHR Exeter Clinical Research Facility. This work has been supported by EFSD/Novo Nordisk. The research was supported by the National Institute for Health Research (NIHR) Exeter Clinical Research Facility. We gratefully acknowledge Dr. Harald Grallert and Dr. Jennifer Kriebel (both Helmholtz Center Munich) for genotyping the TÜF samples. This research has been conducted using the UK Biobank resource. This work was carried out under UK Biobank project numbers 9072, 9055 and 9914. Details of patient and public involvement in the UK Biobank are available online (http://www.ukbiobank.ac.uk/about-biobank-uk/ and https://www.ukbiobank.ac.uk/wp-content/uploads/2011/07/Summary-EGF-consultation.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6). No patients were specifically involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of this study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants, but the UK Biobank disseminates key findings from projects on its website. The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank the NEO study group, Pat van Beelen, Petra Noordijk and Ingeborg de Jonge for the coordination, lab and data management of the NEO study. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze.

Author Contributions: Designed, led the study and wrote the manuscript: HY. Quality-controlled the data in UK Biobank: JT, SEJ, RNB, ARW, MAT, KSR, AM, RMF, MNW, HY, TMF. Performed statistical analysis/provided data in UK Biobank (YJ, HY, AMY, JDB, AIB), NEO (DOM-K, RDM), IMI-DIRECT (FF, ELT, NAP, AM, PF, KVA, EP, JDB), TUF (HS, JM, HUH, NS), GenScotland (YJ, AC, CH), EXTEND (YJ, ATH). All co-authors commented on the manuscript and agreed with the manuscript results and conclusions.

Conflict of interest statement: The authors of this manuscript have the following competing interests: SANOFI employees: Francesca Frau and Karla V. Allebrandt. Other authors have no conflict of interest.

Guarantor Statement: HY is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding:

HY is funded by Diabetes UK RD Lawrence fellowship (grant: 17/0005594). ARW and TMF are supported by the European Research Council (grant 323195:GLUCOSEGENES-FP7-IDEAS-ERC). RNB and RMF are funded by the Wellcome Trust and Royal Society grant 104150/Z/14/Z. JT is funded by the European Regional Development Fund (ERDF) and a Diabetes Research and Wellness Foundation fellowship. SEJ is funded by the Medical Research Council (grant MR/M005070/1). The TÜF study was supported in part by a grant (01GI0925) from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD) and by a grant from the German Research Foundation (DFG KFO114). IMI-DIRECT was supported by the Innovative Medicines Initiative

Joint Undertaking under grant agreement n°115317 (DIRECT), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. Dennis Mook-Kanamori is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023). Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL) Reference 104036/Z/14/Z).

The funders had no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Tables

Table 1. The effect of "favourable adiposity" genetic score on measures of adiposity and cardiometabolic disease outcome in the UK Biobank study. Effects are per carrying additional adiposity allele. 95% CI: 95% confidence interval; P: p-value; N: number; OR: odds ratio.

		14 SNPs			7 "additional" SNPs			
Trait/disease	**Analysis**	**Effect**	**95% CI**	**P**	**Effect**	**95% CI**	**P**	**N (cases vs. controls)**
Body fat %	ALL	0.17	0.169, 0.171	$6x10^{-263}$	0.15	0.149, 0.151	$1x10^{-105}$	443,000
	Women	0.15	0.148, 0.152	$3.5x10^{-116}$	0.14	0.138, 0.142	$8.9x10^{-52}$	240,882
	Men	0.19	0.188, 0.192	$1x10^{-165}$	0.16	0.158, 0.162	$3x10^{-61}$	202,118
BMI (kg/m^2)	ALL	0.040	0.039, 0.041	$3.6x10^{-45}$	0.045	0.044, 0.047	$4.5x10^{-30}$	449,359
	Women	0.041	0.039, 0.042	$3x10^{-28}$	0.047	0.045, 0.049	$1.9x10^{-19}$	243,797
	Men	0.039	0.038, 0.041	$1.6x10^{-22}$	0.042	0.040, 0.045	$6x10^{-14}$	205,528
Type 2 diabetes (OR)	ALL	0.954	0.948, 0.960	$4x10^{-44}$	0.966	0.957, 0.975	$1.9x10^{-13}$	14,371 vs. 428,017
	Women	0.950	0.939, 0.961	$3x10^{-18}$	0.962	0.946, 0.977	$2x10^{-6}$	4,713 vs. 236,073
	Men	0.960	0.948, 0.964	$5x10^{-26}$	0.966	0.955, 0.978	$1x10^{-8}$	9,076 vs. 192,344
Heart disease (OR)	ALL	0.984	0.980, 0.989	$3x10^{-14}$	0.982	0.976, 0.988	$1.5x10^{-9}$	37,741 vs. 318,892
	Women	0.987	0.980, 0.994	0.0003	0.981	0.971, 0.991	0.0003	12,270 vs. 184,550
	Men	0.982	0.977, 0.987	$2x10^{-11}$	0.983	0.975, 0.990	$2.6x10^{-6}$	25,363 vs. 134,433
Hypertension (OR)	ALL	0.987	0.985, 0.989	$1x10^{-33}$	0.989	0.986, 0.992	$3x10^{-13}$	241,691 vs. 206,525
	Women	0.988	0.985, 0.991	$2x10^{-16}$	0.989	0.985, 0.993	$3x10^{-7}$	114,713 vs. 128,623
	Men	0.985	0.981, 0.988	$1.7x10^{-19}$	0.987	0.983, 0.992	$1.6x10^{-7}$	126,978 vs. 77,902
Systolic blood pressure (mmHg)	ALL	-0.173	-0.174, -0.172	$9x10^{-46}$	-0.139	-0.141, -0.138	$3.6x10^{-16}$	450,075
	Women	-0.163	-0.165, -0.162	$1x10^{-22}$	-0.134	-0.136, -0.132	$1x10^{-8}$	244,183
	Men	-0.206	-0.208, -0.205	$7.9x10^{-27}$	-0.161	-0.163, -0.159	$2x10^{-9}$	205,892
Diastolic blood pressure (mmHg)	ALL	-0.074	-0.075, -0.073	$7x10^{-24}$	-0.085	-0.087, -0.083	$1x10^{-16}$	449,322
	Women	-0.078	-0.080, -0.077	$1.6x10^{-14}$	-0.093	-0.095, -0.091	$1x10^{-10}$	243,732
	Men	-0.073	-0.074, -0.071	$1.9x10^{-10}$	-0.081	-0.083, -0.079	$3.5x10^{-7}$	205,590

Table 2. The effect of "favourable adiposity" genetic score on (MRI/CT scan) measures of abdominal adipose tissue using data from 5 studies.

Effects are per carrying additional adiposity allele. 95% CI: 95% confidence interval; P het: P of heterogeneity test across the 5 studies.

		14 SNPs				7 "additional" SNPs			
	Analysis	**Beta**	**95% CI**	**P**	**P het**	**Beta**	**95% CI**	**P**	**P het**
Subcutaneous adipose tissue (Litres)	**All**	0.054	0.042, 0.067	$2x10^{-14}$	0.36	0.048	0.029, 0.067	$9.6x10^{-7}$	0.38
	Women	0.032	0.016, 0.048	$6x10^{-5}$	0.55	0.032	0.010, 0.054	$3x10^{-3}$	0.89
	Men	0.051	0.035, 0.067	$2.5x10^{-11}$	0.16	0.045	0.022, 0.064	$4.9x10^{-5}$	0.35
Visceral adipose tissue (Litres)	**All**	0.005	-0.007, 0.014	0.4	0.69	-0.002	-0.016, 0.011	0.84	0.94
	Women	-0.007	-0.018, 0.005	0.2	0.28	-0.009	-0.025, 0.005	0.21	0.6
	Men	0.011	0.000, 0.020	0.05	0.05	0.007	-0.009, 0.020	0.43	0.34
VATSAT ratio	**All**	-0.005	-0.007, -0.004	$2x10^{-14}$	0.15	-0.005	-0.008, -0.004	$4x10^{-9}$	0.75
	Women	-0.005	-0.007, -0.003	$1x10^{-10}$	0.46	-0.006	-0.008, -0.004	$9x10^{-8}$	0.93
	Men	-0.004	-0.005, -0.002	$7x10^{-7}$	0.03	-0.004	-0.006, -0.002	$4x10^{-4}$	0.16
Liver fat (%)	**All**	-0.087	-0.124, -0.051	$5.6x10^{-6}$	0.015	-0.060	-0.115, -0.009	0.02	0.015
	Women	-0.170	-0.225, -0.110	$6.3x10^{-9}$	0.26	-0.133	-0.216, -0.055	$1x10^{-3}$	0.57
	Men	-0.005	-0.055, 0.041	0.8	0.16	0.000	-0.069, 0.069	0.99	0.086

Figures

Figure 1. Carrying more "favourable adiposity" alleles was associated with higher adiposity but lower risk of type 2 diabetes (**a**), heart disease (**b**) and hypertension (**c**). We divided individuals from UK Biobank into 10 centiles based on their "favourable adiposity" genetic score (x vector). The distribution of "favourable adiposity" genetic score is shown in black and the case/control proportion is shown in red per each centile.

Figure 2. The individual variants were associated with heterogeneous effects on waist-to-hip ratio. Most notably, for two variants, those in/near *PPARG* and *ANKRD55*, the "favourable adiposity" allele was not associated with lower waist-to-hip ratio in women, and for *ANKRD55*, it was associated with higher waist-to-hip ratio. For eleven variants (those in/near *IRS1, TRIB1, CITED2, FAM13A, VEGFA, AEBP2, KLF14, LYPLAL1, DNAH10, MAFF* and *GRB14*) the "favourable adiposity" allele was associated with lower waist-to-hip ratio in women, whilst for the variant in/near PEPD there was no clear association with waist-to-hip ratio in either sex. The x vector illustrates the effect on body fat % in men (right plot) and women (left plot). The y vector illustrates the effect on waist-to-hip ratio. Data is from UK Biobank population.

Figure 3. The effect of "favourable adiposity" genetic score on (MRI/CT scan) measures of abdominal adipose tissue using data from 5 studies. The x-axis is the effect size per carrying additional "favourable adiposity" allele.

References

1. Andres R: Effect of obesity on total mortality. Int J Obes 1980;4:381-386
2. Stefan N, Haring HU, Hu FB, Schulze MB: Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. The lancet Diabetes & endocrinology 2013;1:152-162
3. Ruderman NB, Berchtold P, Schneider S: Obesity-associated disorders in normal-weight individuals: some speculations. Int J Obes 1982;6 Suppl 1:151-157
4. Ruderman NB, Schneider SH, Berchtold P: The "metabolically-obese," normal-weight individual. The American journal of clinical nutrition 1981;34:1617-1621
5. Stefan N, Schick F, Haring HU: Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell metabolism 2017;26:292-300
6. Yaghootkar H, Lotta LA, Tyrrell J, Smit RA, Jones SE, Donnelly L, Beaumont R, Campbell A, Tuke MA, Hayward C, Ruth KS, Padmanabhan S, Jukema JW, Palmer CC, Hattersley A, Freathy RM, Langenberg C, Wareham NJ, Wood AR, Murray A, Weedon MN, Sattar N, Pearson E, Scott RA, Frayling TM: Genetic Evidence for a Link Between Favorable Adiposity and Lower Risk of Type 2 Diabetes, Hypertension, and Heart Disease. Diabetes 2016;65:2448-2460
7. Yaghootkar H, Scott RA, White CC, Zhang W, Speliotes E, Munroe PB, Ehret GB, Bis JC, Fox CS, Walker M, Borecki IB, Knowles JW, Yerges-Armstrong L, Ohlsson C, Perry JR, Chambers JC, Kooner JS, Franceschini N, Langenberg C, Hivert MF, Dastani Z, Richards JB, Semple RK, Frayling TM: Genetic evidence for a normal-weight "metabolically obese" phenotype linking insulin resistance, hypertension, coronary artery disease, and type 2 diabetes. Diabetes 2014;63:4369-4377
8. Kilpelainen TO, Zillikens MC, Stancakova A, Finucane FM, Ried JS, Langenberg C, Zhang W, Beckmann JS, Luan J, Vandenput L, Styrkarsdottir U, Zhou Y, Smith AV, Zhao JH, Amin N, Vedantam S, Shin SY, Haritunians T, Fu M, Feitosa MF, Kumari M, Halldorsson BV, Tikkanen E, Mangino M, Hayward C, Song C, Arnold AM, Aulchenko YS, Oostra BA, Campbell H, Cupples LA, Davis KE, Doring A, Eiriksdottir G, Estrada K, Fernandez-Real JM, Garcia M, Gieger C, Glazer NL, Guiducci C, Hofman A, Humphries SE, Isomaa B, Jacobs LC, Jula A, Karasik D, Karlsson MK, Khaw KT, Kim LJ, Kivimaki M, Klopp N, Kuhnel B, Kuusisto J, Liu Y, Ljunggren O, Lorentzon M, Luben RN, McKnight B, Mellstrom D, Mitchell BD, Mooser V, Moreno JM, Mannisto S, O'Connell JR, Pascoe L, Peltonen L, Peral B, Perola M, Psaty BM, Salomaa V, Savage DB, Semple RK, Skaric-Juric T, Sigurdsson G, Song KS, Spector TD, Syvanen AC, Talmud PJ, Thorleifsson G, Thorsteinsdottir U, Uitterlinden AG, van Duijn CM, Vidal-Puig A, Wild SH, Wright AF, Clegg DJ, Schadt E, Wilson JF, Rudan I, Ripatti S, Borecki IB, Shuldiner AR, Ingelsson E, Jansson JO, Kaplan RC, Gudnason V, Harris TB, Groop L, Kiel DP, Rivadeneira F, Walker M, Barroso I, Vollenweider P, Waeber G, Chambers JC, Kooner JS, Soranzo N, Hirschhorn JN, Stefansson K, Wichmann HE, Ohlsson C, O'Rahilly S, Wareham NJ, Speliotes EK, Fox CS, Laakso M, Loos RJ: Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nature genetics 2011;43:753-760
9. Lotta LA, Gulati P, Day FR, Payne F, Ongen H, van de Bunt M, Gaulton KJ, Eicher JD, Sharp SJ, Luan J, De Lucia Rolfe E, Stewart ID, Wheeler E, Willems SM, Adams C, Yaghootkar H, Forouhi NG, Khaw KT, Johnson AD, Semple RK, Frayling T, Perry JR, Dermitzakis E, McCarthy MI, Barroso I, Wareham NJ, Savage DB, Langenberg C, O'Rahilly S, Scott RA: Integrative genomic analysis implicates limited peripheral

adipose storage capacity in the pathogenesis of human insulin resistance. Nature genetics 2017;49:17-26
10. Scott RA, Fall T, Pasko D, Barker A, Sharp SJ, Arriola L, Balkau B, Barricarte A, Barroso I, Boeing H, Clavel-Chapelon F, Crowe FL, Dekker JM, Fagherazzi G, Ferrannini E, Forouhi NG, Franks PW, Gavrila D, Giedraitis V, Grioni S, Groop LC, Kaaks R, Key TJ, Kuhn T, Lotta LA, Nilsson PM, Overvad K, Palli D, Panico S, Quiros JR, Rolandsson O, Roswall N, Sacerdote C, Sala N, Sanchez MJ, Schulze MB, Siddiq A, Slimani N, Sluijs I, Spijkerman AM, Tjonneland A, Tumino R, van der AD, Yaghootkar H, McCarthy MI, Semple RK, Riboli E, Walker M, Ingelsson E, Frayling TM, Savage DB, Langenberg C, Wareham NJ: Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independent of obesity. Diabetes 2014;63:4378-4387
11. Gray SL, Vidal-Puig AJ: Adipose tissue expandability in the maintenance of metabolic homeostasis. Nutr Rev 2007;65:S7-12
12. Roemmich JN, Rogol AD: Hormonal changes during puberty and their relationship to fat distribution. Am J Hum Biol 1999;11:209-224
13. Collins R: What makes UK Biobank special? Lancet 2012;379:1173-1174
14. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjalmsson BJ, Finucane HK, Salem RM, Chasman DI, Ridker PM, Neale BM, Berger B, Patterson N, Price AL: Efficient Bayesian mixed-model analysis increases association power in large cohorts. Nature genetics 2015;47:284-290
15. Lu Y, Day FR, Gustafsson S, Buchkovich ML, Na J, Bataille V, Cousminer DL, Dastani Z, Drong AW, Esko T, Evans DM, Falchi M, Feitosa MF, Ferreira T, Hedman AK, Haring R, Hysi PG, Iles MM, Justice AE, Kanoni S, Lagou V, Li R, Li X, Locke A, Lu C, Magi R, Perry JR, Pers TH, Qi Q, Sanna M, Schmidt EM, Scott WR, Shungin D, Teumer A, Vinkhuyzen AA, Walker RW, Westra HJ, Zhang M, Zhang W, Zhao JH, Zhu Z, Afzal U, Ahluwalia TS, Bakker SJ, Bellis C, Bonnefond A, Borodulin K, Buchman AS, Cederholm T, Choh AC, Choi HJ, Curran JE, de Groot LC, De Jager PL, Dhonukshe-Rutten RA, Enneman AW, Eury E, Evans DS, Forsen T, Friedrich N, Fumeron F, Garcia ME, Gartner S, Han BG, Havulinna AS, Hayward C, Hernandez D, Hillege H, Ittermann T, Kent JW, Kolcic I, Laatikainen T, Lahti J, Mateo Leach I, Lee CG, Lee JY, Liu T, Liu Y, Lobbens S, Loh M, Lyytikainen LP, Medina-Gomez C, Michaelsson K, Nalls MA, Nielson CM, Oozageer L, Pascoe L, Paternoster L, Polasek O, Ripatti S, Sarzynski MA, Shin CS, Narancic NS, Spira D, Srikanth P, Steinhagen-Thiessen E, Sung YJ, Swart KM, Taittonen L, Tanaka T, Tikkanen E, van der Velde N, van Schoor NM, Verweij N, Wright AF, Yu L, Zmuda JM, Eklund N, Forrester T, Grarup N, Jackson AU, Kristiansson K, Kuulasmaa T, Kuusisto J, Lichtner P, Luan J, Mahajan A, Mannisto S, Palmer CD, Ried JS, Scott RA, Stancakova A, Wagner PJ, Demirkan A, Doring A, Gudnason V, Kiel DP, Kuhnel B, Mangino M, McKnight B, Menni C, O'Connell JR, Oostra BA, Shuldiner AR, Song K, Vandenput L, van Duijn CM, Vollenweider P, White CC, Boehnke M, Boettcher Y, Cooper RS, Forouhi NG, Gieger C, Grallert H, Hingorani A, Jorgensen T, Jousilahti P, Kivimaki M, Kumari M, Laakso M, Langenberg C, Linneberg A, Luke A, McKenzie CA, Palotie A, Pedersen O, Peters A, Strauch K, Tayo BO, Wareham NJ, Bennett DA, Bertram L, Blangero J, Bluher M, Bouchard C, Campbell H, Cho NH, Cummings SR, Czerwinski SA, Demuth I, Eckardt R, Eriksson JG, Ferrucci L, Franco OH, Froguel P, Gansevoort RT, Hansen T, Harris TB, Hastie N, Heliovaara M, Hofman A, Jordan JM, Jula A, Kahonen M, Kajantie E, Knekt PB, Koskinen S, Kovacs P, Lehtimaki T, Lind L, Liu Y, Orwoll ES, Osmond C, Perola M, Perusse L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Rivadeneira F, Rudan I, Salomaa V, Sorensen TI, Stumvoll M, Tonjes A, Towne B,

Tranah GJ, Tremblay A, Uitterlinden AG, van der Harst P, Vartiainen E, Viikari JS, Vitart V, Vohl MC, Volzke H, Walker M, Wallaschofski H, Wild S, Wilson JF, Yengo L, Bishop DT, Borecki IB, Chambers JC, Cupples LA, Dehghan A, Deloukas P, Fatemifar G, Fox C, Furey TS, Franke L, Han J, Hunter DJ, Karjalainen J, Karpe F, Kaplan RC, Kooner JS, McCarthy MI, Murabito JM, Morris AP, Bishop JA, North KE, Ohlsson C, Ong KK, Prokopenko I, Richards JB, Schadt EE, Spector TD, Widen E, Willer CJ, Yang J, Ingelsson E, Mohlke KL, Hirschhorn JN, Pospisilik JA, Zillikens MC, Lindgren C, Kilpelainen TO, Loos RJ: New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. Nat Commun 2016;7:10495
16. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA, Jr., Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S: Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010;466:707-713
17. Dastani Z, Hivert MF, Timpson N, Perry JR, Yuan X, Scott RA, Henneman P, Heid IM, Kizer JR, Lyytikainen LP, Fuchsberger C, Tanaka T, Morris AP, Small K, Isaacs A, Beekman M, Coassin S, Lohman K, Qi L, Kanoni S, Pankow JS, Uh HW, Wu Y, Bidulescu A, Rasmussen-Torvik LJ, Greenwood CM, Ladouceur M, Grimsby J, Manning AK, Liu CT, Kooner J, Mooser VE, Vollenweider P, Kapur KA, Chambers J, Wareham NJ, Langenberg C, Frants R, Willems-Vandijk K, Oostra BA, Willems SM, Lamina C, Winkler TW, Psaty BM, Tracy RP, Brody J, Chen I, Viikari J, Kahonen M, Pramstaller PP, Evans DM, St Pourcain B, Sattar N, Wood AR, Bandinelli S, Carlson

OD, Egan JM, Bohringer S, van Heemst D, Kedenko L, Kristiansson K, Nuotio ML, Loo BM, Harris T, Garcia M, Kanaya A, Haun M, Klopp N, Wichmann HE, Deloukas P, Katsareli E, Couper DJ, Duncan BB, Kloppenburg M, Adair LS, Borja JB, Wilson JG, Musani S, Guo X, Johnson T, Semple R, Teslovich TM, Allison MA, Redline S, Buxbaum SG, Mohlke KL, Meulenbelt I, Ballantyne CM, Dedoussis GV, Hu FB, Liu Y, Paulweber B, Spector TD, Slagboom PE, Ferrucci L, Jula A, Perola M, Raitakari O, Florez JC, Salomaa V, Eriksson JG, Frayling TM, Hicks AA, Lehtimaki T, Smith GD, Siscovick DS, Kronenberg F, van Duijn C, Loos RJ, Waterworth DM, Meigs JB, Dupuis J, Richards JB, Voight BF, Scott LJ, Steinthorsdottir V, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Hofmann OM, Segre AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bostrom KB, Bravenboer B, Bumpstead S, Burtt NP, Charpentier G, Chines PS, Cornelis M, Crawford G, Doney AS, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves CJ, Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PR, Jorgensen T, Kao WH, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Petersen AK, Platou C, Proenca C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shrader P, Sigurdsson G, Sparso T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haeften TW, van Herpt T, van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllensten U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Morris AD, Palmer CN, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Pedersen O, Barroso I, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI, Soranzo N, Wheeler E, Glazer NL, Bouatia-Naji N, Magi R, Randall J, Elliott P, Rybin D, Dehghan A, Hottenga JJ, Song K, Goel A, Lajunen T, Doney A, Cavalcanti-Proenca C, Kumari M, Timpson NJ, Zabena C, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Roccasecca RM, Pattou F, Sethupathy P, Ariyurek Y, Barter P, Beilby JP, Ben-Shlomo Y, Bergmann S, Bochud M, Bonnefond A, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Crisponi L, Day IN, de Geus EJ, Delplanque J, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Grundy S, Gwilliam R, Hallmans G, Hammond N, Han X, Hartikainen AL, Hayward C, Heath SC, Hercberg S, Hillman DR, Hingorani AD, Hui J, Hung J, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Mahley R, Mangino M, Martinez-Larrad MT, McAteer JB, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Mukherjee S, Naitza S, Neville MJ, Orru M, Pakyz R, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tonjes A, Uitterlinden AG, van Dijk KW, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Ward KL, Watkins H, Wild SH, Willemsen G,

Witteman JC, Yarnell JW, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Meneton P, Magnusson PK, Nathan DM, Williams GH, Silander K, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Serrano-Rios M, Lind L, Palmer LJ, Hu FBs, Franks PW, Ebrahim S, Marmot M, Kao WH, Pramstaller PP, Wright AF, Stumvoll M, Hamsten A, Buchanan TA, Valle TT, Rotter JI, Penninx BW, Boomsma DI, Cao A, Scuteri A, Schlessinger D, Uda M, Ruokonen A, Jarvelin MR, Peltonen L, Mooser V, Sladek R, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Chasman DI, Johansen CT, Fouchier SW, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Feitosa MF, Orho-Melander M, Melander O, Li X, Li M, Cho YS, Go MJ, Kim YJ, Lee JY, Park T, Kim K, Sim X, Ong RT, Croteau-Chonka DC, Lange LA, Smith JD, Ziegler A, Zhang W, Zee RY, Whitfield JB, Thompson JR, Surakka I, Spector TD, Smit JH, Sinisalo J, Scott J, Saharinen J, Sabatti C, Rose LM, Roberts R, Rieder M, Parker AN, Pare G, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, McArdle W, Masson D, Martin NG, Marroni F, Lucas G, Luben R, Lokki ML, Lettre G, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Konig IR, Khaw KT, Kaplan LM, Johansson A, Janssens AC, Igl W, Hovingh GK, Hengstenberg C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Groop LC, Gonzalez E, Freimer NB, Erdmann J, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Faire U, Crawford G, Chen YD, Caulfield MJ, Boekholdt SM, Assimes TL, Quertermous T, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Taylor HA, Jr., Gabriel SB, Holm H, Gudnason V, Krauss RM, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Strachan DP, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, Kathiresan S: Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. PLoS Genet 2012;8:e1002607

18. Coviello AD, Haring R, Wellons M, Vaidya D, Lehtimaki T, Keildson S, Lunetta KL, He C, Fornage M, Lagou V, Mangino M, Onland-Moret NC, Chen B, Eriksson J, Garcia M, Liu YM, Koster A, Lohman K, Lyytikainen LP, Petersen AK, Prescott J, Stolk L, Vandenput L, Wood AR, Zhuang WV, Ruokonen A, Hartikainen AL, Pouta A, Bandinelli S, Biffar R, Brabant G, Cox DG, Chen Y, Cummings S, Ferrucci L, Gunter MJ, Hankinson SE, Martikainen H, Hofman A, Homuth G, Illig T, Jansson JO, Johnson AD, Karasik D, Karlsson M, Kettunen J, Kiel DP, Kraft P, Liu J, Ljunggren O, Lorentzon M, Maggio M, Markus MR, Mellstrom D, Miljkovic I, Mirel D, Nelson S, Morin Papunen L, Peeters PH, Prokopenko I, Raffel L, Reincke M, Reiner AP, Rexrode K, Rivadeneira F, Schwartz SM, Siscovick D, Soranzo N, Stockl D, Tworoger S, Uitterlinden AG, van Gils CH, Vasan RS, Wichmann HE, Zhai G, Bhasin S, Bidlingmaier M, Chanock SJ, De Vivo I, Harris TB, Hunter DJ, Kahonen M, Liu S, Ouyang P, Spector TD, van der Schouw YT, Viikari J, Wallaschofski H, McCarthy MI, Frayling TM, Murray A, Franks S, Jarvelin MR, de Jong FH, Raitakari O, Teumer A, Ohlsson C, Murabito JM, Perry JR: A genome-wide association meta-analysis of circulating sex hormone-binding globulin reveals multiple Loci implicated in sex steroid hormone regulation. PLoS Genet 2012;8:e1002805

19. Manning AK, Hivert MF, Scott RA, Grimsby JL, Bouatia-Naji N, Chen H, Rybin D, Liu CT, Bielak LF, Prokopenko I, Amin N, Barnes D, Cadby G, Hottenga JJ, Ingelsson E, Jackson AU, Johnson T, Kanoni S, Ladenvall C, Lagou V, Lahti J, Lecoeur C, Liu Y, Martinez-Larrad MT, Montasser ME, Navarro P, Perry JR, Rasmussen-Torvik LJ, Salo P, Sattar N, Shungin D, Strawbridge RJ, Tanaka T, van Duijn CM, An P, de Andrade M, Andrews JS, Aspelund T, Atalay M, Aulchenko Y, Balkau B, Bandinelli S, Beckmann JS, Beilby JP, Bellis C, Bergman RN, Blangero J, Boban M,

Boehnke M, Boerwinkle E, Bonnycastle LL, Boomsma DI, Borecki IB, Bottcher Y, Bouchard C, Brunner E, Budimir D, Campbell H, Carlson O, Chines PS, Clarke R, Collins FS, Corbaton-Anchuelo A, Couper D, de Faire U, Dedoussis GV, Deloukas P, Dimitriou M, Egan JM, Eiriksdottir G, Erdos MR, Eriksson JG, Eury E, Ferrucci L, Ford I, Forouhi NG, Fox CS, Franzosi MG, Franks PW, Frayling TM, Froguel P, Galan P, de Geus E, Gigante B, Glazer NL, Goel A, Groop L, Gudnason V, Hallmans G, Hamsten A, Hansson O, Harris TB, Hayward C, Heath S, Hercberg S, Hicks AA, Hingorani A, Hofman A, Hui J, Hung J, Jarvelin MR, Jhun MA, Johnson PC, Jukema JW, Jula A, Kao WH, Kaprio J, Kardia SL, Keinanen-Kiukaanniemi S, Kivimaki M, Kolcic I, Kovacs P, Kumari M, Kuusisto J, Kyvik KO, Laakso M, Lakka T, Lannfelt L, Lathrop GM, Launer LJ, Leander K, Li G, Lind L, Lindstrom J, Lobbens S, Loos RJ, Luan J, Lyssenko V, Magi R, Magnusson PK, Marmot M, Meneton P, Mohlke KL, Mooser V, Morken MA, Miljkovic I, Narisu N, O'Connell J, Ong KK, Oostra BA, Palmer LJ, Palotie A, Pankow JS, Peden JF, Pedersen NL, Pehlic M, Peltonen L, Penninx B, Pericic M, Perola M, Perusse L, Peyser PA, Polasek O, Pramstaller PP, Province MA, Raikkonen K, Rauramaa R, Rehnberg E, Rice K, Rotter JI, Rudan I, Ruokonen A, Saaristo T, Sabater-Lleal M, Salomaa V, Savage DB, Saxena R, Schwarz P, Seedorf U, Sennblad B, Serrano-Rios M, Shuldiner AR, Sijbrands EJ, Siscovick DS, Smit JH, Small KS, Smith NL, Smith AV, Stancakova A, Stirrups K, Stumvoll M, Sun YV, Swift AJ, Tonjes A, Tuomilehto J, Trompet S, Uitterlinden AG, Uusitupa M, Vikstrom M, Vitart V, Vohl MC, Voight BF, Vollenweider P, Waeber G, Waterworth DM, Watkins H, Wheeler E, Widen E, Wild SH, Willems SM, Willemsen G, Wilson JF, Witteman JC, Wright AF, Yaghootkar H, Zelenika D, Zemunik T, Zgaga L, Wareham NJ, McCarthy MI, Barroso I, Watanabe RM, Florez JC, Dupuis J, Meigs JB, Langenberg C: A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. Nature genetics 2012;44:659-669

20. Chambers JC, Zhang W, Sehmi J, Li X, Wass MN, Van der Harst P, Holm H, Sanna S, Kavousi M, Baumeister SE, Coin LJ, Deng G, Gieger C, Heard-Costa NL, Hottenga JJ, Kuhnel B, Kumar V, Lagou V, Liang L, Luan J, Vidal PM, Mateo Leach I, O'Reilly PF, Peden JF, Rahmioglu N, Soininen P, Speliotes EK, Yuan X, Thorleifsson G, Alizadeh BZ, Atwood LD, Borecki IB, Brown MJ, Charoen P, Cucca F, Das D, de Geus EJ, Dixon AL, Doring A, Ehret G, Eyjolfsson GI, Farrall M, Forouhi NG, Friedrich N, Goessling W, Gudbjartsson DF, Harris TB, Hartikainen AL, Heath S, Hirschfield GM, Hofman A, Homuth G, Hypponen E, Janssen HL, Johnson T, Kangas AJ, Kema IP, Kuhn JP, Lai S, Lathrop M, Lerch MM, Li Y, Liang TJ, Lin JP, Loos RJ, Martin NG, Moffatt MF, Montgomery GW, Munroe PB, Musunuru K, Nakamura Y, O'Donnell CJ, Olafsson I, Penninx BW, Pouta A, Prins BP, Prokopenko I, Puls R, Ruokonen A, Savolainen MJ, Schlessinger D, Schouten JN, Seedorf U, Sen-Chowdhry S, Siminovitch KA, Smit JH, Spector TD, Tan W, Teslovich TM, Tukiainen T, Uitterlinden AG, Van der Klauw MM, Vasan RS, Wallace C, Wallaschofski H, Wichmann HE, Willemsen G, Wurtz P, Xu C, Yerges-Armstrong LM, Abecasis GR, Ahmadi KR, Boomsma DI, Caulfield M, Cookson WO, van Duijn CM, Froguel P, Matsuda K, McCarthy MI, Meisinger C, Mooser V, Pietilainen KH, Schumann G, Snieder H, Sternberg MJ, Stolk RP, Thomas HC, Thorsteinsdottir U, Uda M, Waeber G, Wareham NJ, Waterworth DM, Watkins H, Whitfield JB, Witteman JC, Wolffenbuttel BH, Fox CS, Ala-Korpela M, Stefansson K, Vollenweider P, Volzke H, Schadt EE, Scott J, Jarvelin MR, Elliott P, Kooner JS: Genome-wide association study identifies loci influencing concentrations of liver enzymes in plasma. Nature genetics 2011;43:1131-1138

21. Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S: Genetic syndromes of severe insulin resistance. Endocrine reviews 2011;32:498-514
22. Stears A, O'Rahilly S, Semple RK, Savage DB: Metabolic insights from extreme human insulin resistance phenotypes. Best practice & research Clinical endocrinology & metabolism 2012;26:145-157
23. Cichonska A, Rousu J, Marttinen P, Kangas AJ, Soininen P, Lehtimaki T, Raitakari OT, Jarvelin MR, Salomaa V, Ala-Korpela M, Ripatti S, Pirinen M: metaCCA: summary statistics-based multivariate meta-analysis of genome-wide association studies using canonical correlation analysis. Bioinformatics 2016;32:1981-1989
24. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, de Roos A, Cobbaert CM, Kloppenburg M, le Cessie S, Middeldorp S, Rosendaal FR: The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-523
25. Smith BH, Campbell A, Linksted P, Fitzpatrick B, Jackson C, Kerr SM, Deary IJ, Macintyre DJ, Campbell H, McGilchrist M, Hocking LJ, Wisely L, Ford I, Lindsay RS, Morton R, Palmer CN, Dominiczak AF, Porteous DJ, Morris AD: Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. Int J Epidemiol 2013;42:689-700
26. Machann J, Thamer C, Stefan N, Schwenzer NF, Kantartzis K, Haring HU, Claussen CD, Fritsche A, Schick F: Follow-up whole-body assessment of adipose tissue compartments during a lifestyle intervention in a large cohort at increased risk for type 2 diabetes. Radiology 2010;257:353-363
27. Koivula RW, Heggie A, Barnett A, Cederberg H, Hansen TH, Koopman AD, Ridderstrale M, Rutters F, Vestergaard H, Gupta R, Herrgard S, Heymans MW, Perry MH, Rauh S, Siloaho M, Teare HJ, Thorand B, Bell J, Brunak S, Frost G, Jablonka B, Mari A, McDonald TJ, Dekker JM, Hansen T, Hattersley A, Laakso M, Pedersen O, Koivisto V, Ruetten H, Walker M, Pearson E, Franks PW: Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: rationale and design of the epidemiological studies within the IMI DIRECT Consortium. Diabetologia 2014;57:1132-1142
28. Mahajan A, Go MJ, Zhang W, Below JE, Gaulton KJ, Ferreira T, Horikoshi M, Johnson AD, Ng MC, Prokopenko I, Saleheen D, Wang X, Zeggini E, Abecasis GR, Adair LS, Almgren P, Atalay M, Aung T, Baldassarre D, Balkau B, Bao Y, Barnett AH, Barroso I, Basit A, Been LF, Beilby J, Bell GI, Benediktsson R, Bergman RN, Boehm BO, Boerwinkle E, Bonnycastle LL, Burtt N, Cai Q, Campbell H, Carey J, Cauchi S, Caulfield M, Chan JC, Chang LC, Chang TJ, Chang YC, Charpentier G, Chen CH, Chen H, Chen YT, Chia KS, Chidambaram M, Chines PS, Cho NH, Cho YM, Chuang LM, Collins FS, Cornelis MC, Couper DJ, Crenshaw AT, van Dam RM, Danesh J, Das D, de Faire U, Dedoussis G, Deloukas P, Dimas AS, Dina C, Doney AS, Donnelly PJ, Dorkhan M, van Duijn C, Dupuis J, Edkins S, Elliott P, Emilsson V, Erbel R, Eriksson JG, Escobedo J, Esko T, Eury E, Florez JC, Fontanillas P, Forouhi NG, Forsen T, Fox C, Fraser RM, Frayling TM, Froguel P, Frossard P, Gao Y, Gertow K, Gieger C, Gigante B, Grallert H, Grant GB, Grrop LC, Groves CJ, Grundberg E, Guiducci C, Hamsten A, Han BG, Hara K, Hassanali N, Hattersley AT, Hayward C, Hedman AK, Herder C, Hofman A, Holmen OL, Hovingh K, Hreidarsson AB, Hu C, Hu FB, Hui J, Humphries SE, Hunt SE, Hunter DJ, Hveem K, Hydrie ZI, Ikegami H, Illig T, Ingelsson E, Islam M, Isomaa B, Jackson AU, Jafar T, James A, Jia W, Jockel KH, Jonsson A, Jowett JB, Kadowaki T, Kang HM, Kanoni S, Kao WH, Kathiresan S, Kato N, Katulanda P, Keinanen-Kiukaanniemi KM, Kelly AM, Khan H, Khaw KT,

Khor CC, Kim HL, Kim S, Kim YJ, Kinnunen L, Klopp N, Kong A, Korpi-Hyovalti E, Kowlessur S, Kraft P, Kravic J, Kristensen MM, Krithika S, Kumar A, Kumate J, Kuusisto J, Kwak SH, Laakso M, Lagou V, Lakka TA, Langenberg C, Langford C, Lawrence R, Leander K, Lee JM, Lee NR, Li M, Li X, Li Y, Liang J, Liju S, Lim WY, Lind L, Lindgren CM, Lindholm E, Liu CT, Liu JJ, Lobbens S, Long J, Loos RJ, Lu W, Luan J, Lyssenko V, Ma RC, Maeda S, Magi R, Mannisto S, Matthews DR, Meigs JB, Melander O, Metspalu A, Meyer J, Mirza G, Mihailov E, Moebus S, Mohan V, Mohlke KL, Morris AD, Muhleisen TW, Muller-Nurasyid M, Musk B, Nakamura J, Nakashima E, Navarro P, Ng PK, Nica AC, Nilsson PM, Njolstad I, Nothen MM, Ohnaka K, Ong TH, Owen KR, Palmer CN, Pankow JS, Park KS, Parkin M, Pechlivanis S, Pedersen NL, Peltonen L, Perry JR, Peters A, Pinidiyapathirage JM, Platou CG, Potter S, Price JF, Qi L, Radha V, Rallidis L, Rasheed A, Rathman W, Rauramaa R, Raychaudhuri S, Rayner NW, Rees SD, Rehnberg E, Ripatti S, Robertson N, Roden M, Rossin EJ, Rudan I, Rybin D, Saaristo TE, Salomaa V, Saltevo J, Samuel M, Sanghera DK, Saramies J, Scott J, Scott LJ, Scott RA, Segre AV, Sehmi J, Sennblad B, Shah N, Shah S, Shera AS, Shu XO, Shuldiner AR, Sigurdsson G, Sijbrands E, Silveira A, Sim X, Sivapalaratnam S, Small KS, So WY, Stancakova A, Stefansson K, Steinbach G, Steinthorsdottir V, Stirrups K, Strawbridge RJ, Stringham HM, Sun Q, Suo C, Syvanen AC, Takayanagi R, Takeuchi F, Tay WT, Teslovich TM, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tikkanen E, Trakalo J, Tremoli E, Trip MD, Tsai FJ, Tuomi T, Tuomilehto J, Uitterlinden AG, Valladares-Salgado A, Vedantam S, Veglia F, Voight BF, Wang C, Wareham NJ, Wennauer R, Wickremasinghe AR, Wilsgaard T, Wilson JF, Wiltshire S, Winckler W, Wong TY, Wood AR, Wu JY, Wu Y, Yamamoto K, Yamauchi T, Yang M, Yengo L, Yokota M, Young R, Zabaneh D, Zhang F, Zhang R, Zheng W, Zimmet PZ, Altshuler D, Bowden DW, Cho YS, Cox NJ, Cruz M, Hanis CL, Kooner J, Lee JY, Seielstad M, Teo YY, Boehnke M, Parra EJ, Chambers JC, Tai ES, McCarthy MI, Morris AP: Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nature genetics 2014;46:234-244

29. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Huang J, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJF, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ,

Farrall M: A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nature genetics 2015;47:1121-1130
30. Wain LV, Vaez A, Jansen R, Joehanes R, van der Most PJ, Erzurumluoglu AM, O'Reilly PF, Cabrera CP, Warren HR, Rose LM, Verwoert GC, Hottenga JJ, Strawbridge RJ, Esko T, Arking DE, Hwang SJ, Guo X, Kutalik Z, Trompet S, Shrine N, Teumer A, Ried JS, Bis JC, Smith AV, Amin N, Nolte IM, Lyytikainen LP, Mahajan A, Wareham NJ, Hofer E, Joshi PK, Kristiansson K, Traglia M, Havulinna AS, Goel A, Nalls MA, Sober S, Vuckovic D, Luan J, Del Greco MF, Ayers KL, Marrugat J, Ruggiero D, Lopez LM, Niiranen T, Enroth S, Jackson AU, Nelson CP, Huffman JE, Zhang W, Marten J, Gandin I, Harris SE, Zemunik T, Lu Y, Evangelou E, Shah N, de Borst MH, Mangino M, Prins BP, Campbell A, Li-Gao R, Chauhan G, Oldmeadow C, Abecasis G, Abedi M, Barbieri CM, Barnes MR, Batini C, Beilby J, Blake T, Boehnke M, Bottinger EP, Braund PS, Brown M, Brumat M, Campbell H, Chambers JC, Cocca M, Collins F, Connell J, Cordell HJ, Damman JJ, Davies G, de Geus EJ, de Mutsert R, Deelen J, Demirkale Y, Doney ASF, Dorr M, Farrall M, Ferreira T, Franberg M, Gao H, Giedraitis V, Gieger C, Giulianini F, Gow AJ, Hamsten A, Harris TB, Hofman A, Holliday EG, Hui J, Jarvelin MR, Johansson A, Johnson AD, Jousilahti P, Jula A, Kahonen M, Kathiresan S, Khaw KT, Kolcic I, Koskinen S, Langenberg C, Larson M, Launer LJ, Lehne B, Liewald DCM, Lin L, Lind L, Mach F, Mamasoula C, Menni C, Mifsud B, Milaneschi Y, Morgan A, Morris AD, Morrison AC, Munson PJ, Nandakumar P, Nguyen QT, Nutile T, Oldehinkel AJ, Oostra BA, Org E, Padmanabhan S, Palotie A, Pare G, Pattie A, Penninx B, Poulter N, Pramstaller PP, Raitakari OT, Ren M, Rice K, Ridker PM, Riese H, Ripatti S, Robino A, Rotter JI, Rudan I, Saba Y, Saint Pierre A, Sala CF, Sarin AP, Schmidt R, Scott R, Seelen MA, Shields DC, Siscovick D, Sorice R, Stanton A, Stott DJ, Sundstrom J, Swertz M, Taylor KD, Thom S, Tzoulaki I, Tzourio C, Uitterlinden AG, Volker U, Vollenweider P, Wild S, Willemsen G, Wright AF, Yao J, Theriault S, Conen D, Attia J, Sever P, Debette S, Mook-Kanamori DO, Zeggini E, Spector TD, van der Harst P, Palmer CNA, Vergnaud AC, Loos RJF, Polasek O, Starr JM, Girotto G, Hayward C, Kooner JS, Lindgren CM, Vitart V, Samani NJ, Tuomilehto J, Gyllensten U, Knekt P, Deary IJ, Ciullo M, Elosua R, Keavney BD, Hicks AA, Scott RA, Gasparini P, Laan M, Liu Y, Watkins H, Hartman CA, Salomaa V, Toniolo D, Perola M, Wilson JF, Schmidt H, Zhao JH, Lehtimaki T, van Duijn CM, Gudnason V, Psaty BM, Peters A, Rettig R, James A, Jukema JW, Strachan DP, Palmas W, Metspalu A, Ingelsson E, Boomsma DI, Franco OH, Bochud M, Newton-Cheh C, Munroe PB, Elliott P, Chasman DI, Chakravarti A, Knight J, Morris AP, Levy D, Tobin MD, Snieder H, Caulfield MJ, Ehret GB: Novel Blood Pressure Locus and Gene Discovery Using Genome-Wide Association Study and Expression Data Sets From Blood and the Kidney. Hypertension 2017;
31. Wilman HR, Kelly M, Garratt S, Matthews PM, Milanesi M, Herlihy A, Gyngell M, Neubauer S, Bell JD, Banerjee R, Thomas EL: Characterisation of liver fat in the UK Biobank cohort. PloS one 2017;12:e0172921
32. Linge J, Borga M, West J, Tuthill T, Miller MR, Dumitriu A, Thomas EL, Romu T, Tunon P, Bell JD, Dahlqvist Leinhard O: Body Composition Profiling in the UK Biobank Imaging Study. Obesity (Silver Spring, Md) 2018;
33. West J, Dahlqvist Leinhard O, Romu T, Collins R, Garratt S, Bell JD, Borga M, Thomas L: Feasibility of MR-Based Body Composition Analysis in Large Scale Population Studies. PloS one 2016;11:e0163332
34. Thomas EL, Fitzpatrick JA, Malik SJ, Taylor-Robinson SD, Bell JD: Whole body fat: content and distribution. Prog Nucl Magn Reson Spectrosc 2013;73:56-80

35. Chu AY, Deng X, Fisher VA, Drong A, Zhang Y, Feitosa MF, Liu CT, Weeks O, Choh AC, Duan Q, Dyer TD, Eicher JD, Guo X, Heard-Costa NL, Kacprowski T, Kent JW, Jr., Lange LA, Liu X, Lohman K, Lu L, Mahajan A, O'Connell JR, Parihar A, Peralta JM, Smith AV, Zhang Y, Homuth G, Kissebah AH, Kullberg J, Laqua R, Launer LJ, Nauck M, Olivier M, Peyser PA, Terry JG, Wojczynski MK, Yao J, Bielak LF, Blangero J, Borecki IB, Bowden DW, Carr JJ, Czerwinski SA, Ding J, Friedrich N, Gudnason V, Harris TB, Ingelsson E, Johnson AD, Kardia SL, Langefeld CD, Lind L, Liu Y, Mitchell BD, Morris AP, Mosley TH, Jr., Rotter JI, Shuldiner AR, Towne B, Volzke H, Wallaschofski H, Wilson JG, Allison M, Lindgren CM, Goessling W, Cupples LA, Steinhauser ML, Fox CS: Multiethnic genome-wide meta-analysis of ectopic fat depots identifies loci associated with adipocyte development and differentiation. Nature genetics 2017;49:125-130
36. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE, Workalemahu T, Wu JMW, Buchkovich ML, Heard-Costa NL, Roman TS, Drong AW, Song C, Gustafsson S, Day FR, Esko T, Fall T, Kutalik Z, Luan J, Randall JC, Scherag A, Vedantam S, Wood AR, Chen J, Fehrmann R, Karjalainen J, Kahali B, Liu CT, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bragg-Gresham JL, Buyske S, Demirkan A, Ehret GB, Feitosa MF, Goel A, Jackson AU, Johnson T, Kleber ME, Kristiansson K, Mangino M, Leach IM, Medina-Gomez C, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Stancakova A, Sung YJ, Tanaka T, Teumer A, Van Vliet-Ostaptchouk JV, Yengo L, Zhang W, Albrecht E, Arnlov J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Bluher M, Bohringer S, Bonnet F, Bottcher Y, Bruinenberg M, Carba DB, Caspersen IH, Clarke R, Daw EW, Deelen J, Deelman E, Delgado G, Doney AS, Eklund N, Erdos MR, Estrada K, Eury E, Friedrich N, Garcia ME, Giedraitis V, Gigante B, Go AS, Golay A, Grallert H, Grammer TB, Grassler J, Grewal J, Groves CJ, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heikkila K, Herzig KH, Helmer Q, Hillege HL, Holmen O, Hunt SC, Isaacs A, Ittermann T, James AL, Johansson I, Juliusdottir T, Kalafati IP, Kinnunen L, Koenig W, Kooner IK, Kratzer W, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindstrom J, Lobbens S, Lorentzon M, Mach F, Magnusson PK, Mahajan A, McArdle WL, Menni C, Merger S, Mihailov E, Milani L, Mills R, Moayyeri A, Monda KL, Mooijaart SP, Muhleisen TW, Mulas A, Muller G, Muller-Nurasyid M, Nagaraja R, Nalls MA, Narisu N, Glorioso N, Nolte IM, Olden M, Rayner NW, Renstrom F, Ried JS, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Sennblad B, Seufferlein T, Sitlani CM, Smith AV, Stirrups K, Stringham HM, Sundstrom J, Swertz MA, Swift AJ, Syvanen AC, Tayo BO, Thorand B, Thorleifsson G, Tomaschitz A, Troffa C, van Oort FV, Verweij N, Vonk JM, Waite LL, Wennauer R, Wilsgaard T, Wojczynski MK, Wong A, Zhang Q, Zhao JH, Brennan EP, Choi M, Eriksson P, Folkersen L, Franco-Cereceda A, Gharavi AG, Hedman AK, Hivert MF, Huang J, Kanoni S, Karpe F, Keildson S, Kiryluk K, Liang L, Lifton RP, Ma B, McKnight AJ, McPherson R, Metspalu A, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Olsson C, Perry JR, Reinmaa E, Salem RM, Sandholm N, Schadt EE, Scott RA, Stolk L, Vallejo EE, Westra HJ, Zondervan KT, Amouyel P, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Brown MJ, Burnier M, Campbell H, Chakravarti A, Chines PS, Claudi-Boehm S, Collins FS, Crawford DC, Danesh J, de Faire U, de Geus EJ, Dorr M, Erbel R, Eriksson JG, Farrall M, Ferrannini E, Ferrieres J, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gieger C, Gudnason V, Haiman CA, Harris TB, Hattersley AT, Heliovaara M, Hicks AA, Hingorani AD, Hoffmann W, Hofman A, Homuth G, Humphries SE, Hypponen E, Illig

T, Jarvelin MR, Johansen B, Jousilahti P, Jula AM, Kaprio J, Kee F, Keinanen-Kiukaanniemi SM, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuulasmaa K, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimaki T, Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Musk AW, Mohlenkamp S, Morris AD, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Palmer LJ, Penninx BW, Peters A, Pramstaller PP, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schwarz PE, Shuldiner AR, Staessen JA, Steinthorsdottir V, Stolk RP, Strauch K, Tonjes A, Tremblay A, Tremoli E, Vohl MC, Volker U, Vollenweider P, Wilson JF, Witteman JC, Adair LS, Bochud M, Boehm BO, Bornstein SR, Bouchard C, Cauchi S, Caulfield MJ, Chambers JC, Chasman DI, Cooper RS, Dedoussis G, Ferrucci L, Froguel P, Grabe HJ, Hamsten A, Hui J, Hveem K, Jockel KH, Kivimaki M, Kuh D, Laakso M, Liu Y, Marz W, Munroe PB, Njolstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sinisalo J, Slagboom PE, Snieder H, Spector TD, Stefansson K, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Veronesi G, Walker M, Wareham NJ, Watkins H, Wichmann HE, Abecasis GR, Assimes TL, Berndt SI, Boehnke M, Borecki IB, Deloukas P, Franke L, Frayling TM, Groop LC, Hunter DJ, Kaplan RC, O'Connell JR, Qi L, Schlessinger D, Strachan DP, Thorsteinsdottir U, van Duijn CM, Willer CJ, Visscher PM, Yang J, Hirschhorn JN, Zillikens MC, McCarthy MI, Speliotes EK, North KE, Fox CS, Barroso I, Franks PW, Ingelsson E, Heid IM, Loos RJ, Cupples LA, Morris AP, Lindgren CM, Mohlke KL: New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187-196

37. Ley CJ, Lees B, Stevenson JC: Sex- and menopause-associated changes in body-fat distribution. The American journal of clinical nutrition 1992;55:950-954

38. Svendsen OL, Hassager C, Christiansen C: Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metabolism 1995;44:369-373

39. Preiss D, Sattar N: Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. Clin Sci (Lond) 2008;115:141-150

40. Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP: The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. Drug Alcohol Depend 2004;74:223-234

41. Holmila M, Raitasalo K: Gender differences in drinking: why do they still exist? Addiction 2005;100:1763-1769

42. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, Magi R, Strawbridge RJ, Rehnberg E, Gustafsson S, Kanoni S, Rasmussen-Torvik LJ, Yengo L, Lecoeur C, Shungin D, Sanna S, Sidore C, Johnson PC, Jukema JW, Johnson T, Mahajan A, Verweij N, Thorleifsson G, Hottenga JJ, Shah S, Smith AV, Sennblad B, Gieger C, Salo P, Perola M, Timpson NJ, Evans DM, Pourcain BS, Wu Y, Andrews JS, Hui J, Bielak LF, Zhao W, Horikoshi M, Navarro P, Isaacs A, O'Connell JR, Stirrups K, Vitart V, Hayward C, Esko T, Mihailov E, Fraser RM, Fall T, Voight BF, Raychaudhuri S, Chen H, Lindgren CM, Morris AP, Rayner NW, Robertson N, Rybin D, Liu CT, Beckmann JS, Willems SM, Chines PS, Jackson AU, Kang HM, Stringham HM, Song K, Tanaka T, Peden JF, Goel A, Hicks AA, An P, Muller-Nurasyid M, Franco-Cereceda A, Folkersen L, Marullo L, Jansen H, Oldehinkel AJ, Bruinenberg M, Pankow JS, North KE, Forouhi NG, Loos RJ, Edkins S, Varga TV, Hallmans G, Oksa H, Antonella M, Nagaraja R, Trompet S, Ford I, Bakker SJ, Kong A, Kumari M,

Gigante B, Herder C, Munroe PB, Caulfield M, Antti J, Mangino M, Small K, Miljkovic I, Liu Y, Atalay M, Kiess W, James AL, Rivadeneira F, Uitterlinden AG, Palmer CN, Doney AS, Willemsen G, Smit JH, Campbell S, Polasek O, Bonnycastle LL, Hercberg S, Dimitriou M, Bolton JL, Fowkes GR, Kovacs P, Lindstrom J, Zemunik T, Bandinelli S, Wild SH, Basart HV, Rathmann W, Grallert H, Maerz W, Kleber ME, Boehm BO, Peters A, Pramstaller PP, Province MA, Borecki IB, Hastie ND, Rudan I, Campbell H, Watkins H, Farrall M, Stumvoll M, Ferrucci L, Waterworth DM, Bergman RN, Collins FS, Tuomilehto J, Watanabe RM, de Geus EJ, Penninx BW, Hofman A, Oostra BA, Psaty BM, Vollenweider P, Wilson JF, Wright AF, Hovingh GK, Metspalu A, Uusitupa M, Magnusson PK, Kyvik KO, Kaprio J, Price JF, Dedoussis GV, Deloukas P, Meneton P, Lind L, Boehnke M, Shuldiner AR, van Duijn CM, Morris AD, Toenjes A, Peyser PA, Beilby JP, Korner A, Kuusisto J, Laakso M, Bornstein SR, Schwarz PE, Lakka TA, Rauramaa R, Adair LS, Smith GD, Spector TD, Illig T, de Faire U, Hamsten A, Gudnason V, Kivimaki M, Hingorani A, Keinanen-Kiukaanniemi SM, Saaristo TE, Boomsma DI, Stefansson K, van der Harst P, Dupuis J, Pedersen NL, Sattar N, Harris TB, Cucca F, Ripatti S, Salomaa V, Mohlke KL, Balkau B, Froguel P, Pouta A, Jarvelin MR, Wareham NJ, Bouatia-Naji N, McCarthy MI, Franks PW, Meigs JB, Teslovich TM, Florez JC, Langenberg C, Ingelsson E, Prokopenko I, Barroso I: Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nature genetics 2012;44:991-1005

43. Harder MN, Ribel-Madsen R, Justesen JM, Sparso T, Andersson EA, Grarup N, Jorgensen T, Linneberg A, Hansen T, Pedersen O: Type 2 diabetes risk alleles near BCAR1 and in ANK1 associate with decreased beta-cell function whereas risk alleles near ANKRD55 and GRB14 associate with decreased insulin sensitivity in the Danish Inter99 cohort. The Journal of clinical endocrinology and metabolism 2013;98:E801-806

44. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB: Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. The American journal of clinical nutrition 2005;81:555-563

45. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, Balletshofer B, Machicao F, Fritsche A, Haring HU: Identification and characterization of metabolically benign obesity in humans. Arch Intern Med 2008;168:1609-1616

46. Gupta AK, Bray GA, Greenway FL, Martin CK, Johnson WD, Smith SR: Pioglitazone, but not metformin, reduces liver fat in Type-2 diabetes mellitus independent of weight changes. J Diabetes Complications 2010;24:289-296

47. Smith SR, De Jonge L, Volaufova J, Li Y, Xie H, Bray GA: Effect of pioglitazone on body composition and energy expenditure: a randomized controlled trial. Metabolism 2005;54:24-32

48. Satoh T, Kidoya H, Naito H, Yamamoto M, Takemura N, Nakagawa K, Yoshioka Y, Morii E, Takakura N, Takeuchi O, Akira S: Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. Nature 2013;495:524-528

49. Sung HK, Doh KO, Son JE, Park JG, Bae Y, Choi S, Nelson SM, Cowling R, Nagy K, Michael IP, Koh GY, Adamson SL, Pawson T, Nagy A: Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis. Cell metabolism 2013;17:61-72

50. Tien ES, Davis JW, Vanden Heuvel JP: Identification of the CREB-binding protein/p300-interacting protein CITED2 as a peroxisome proliferator-activated receptor alpha coregulator. J Biol Chem 2004;279:24053-24063

51. Wardhana DA, Ikeda K, Barinda AJ, Nugroho DB, Qurania KR, Yagi K, Miyata K, Oike Y, Hirata KI, Emoto N: Family with sequence similarity 13, member A modulates adipocyte insulin signaling and preserves systemic metabolic homeostasis. Proc Natl Acad Sci U S A 2018;115:1529-1534
52. Small KS, Hedman AK, Grundberg E, Nica AC, Thorleifsson G, Kong A, Thorsteindottir U, Shin SY, Richards HB, Soranzo N, Ahmadi KR, Lindgren CM, Stefansson K, Dermitzakis ET, Deloukas P, Spector TD, McCarthy MI: Identification of an imprinted master trans regulator at the KLF14 locus related to multiple metabolic phenotypes. Nature genetics 2011;43:561-564
53. Small KS, Todorcevic M, Civelek M, El-Sayed Moustafa JS, Wang X, Simon MM, Fernandez-Tajes J, Mahajan A, Horikoshi M, Hugill A, Glastonbury CA, Quaye L, Neville MJ, Sethi S, Yon M, Pan C, Che N, Vinuela A, Tsai PC, Nag A, Buil A, Thorleifsson G, Raghavan A, Ding Q, Morris AP, Bell JT, Thorsteinsdottir U, Stefansson K, Laakso M, Dahlman I, Arner P, Gloyn AL, Musunuru K, Lusis AJ, Cox RD, Karpe F, McCarthy MI: Regulatory variants at KLF14 influence type 2 diabetes risk via a female-specific effect on adipocyte size and body composition. Nature genetics 2018;50:572-580
54. Yujiri T, Nawata R, Takahashi T, Sato Y, Tanizawa Y, Kitamura T, Oka Y: MEK kinase 1 interacts with focal adhesion kinase and regulates insulin receptor substrate-1 expression. J Biol Chem 2003;278:3846-3851
55. Steinberg GR, Kemp BE, Watt MJ: Adipocyte triglyceride lipase expression in human obesity. Am J Physiol Endocrinol Metab 2007;293:E958-964
56. Fagerberg L, Hallstrom BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, Habuka M, Tahmasebpoor S, Danielsson A, Edlund K, Asplund A, Sjostedt E, Lundberg E, Szigyarto CA, Skogs M, Takanen JO, Berling H, Tegel H, Mulder J, Nilsson P, Schwenk JM, Lindskog C, Danielsson F, Mardinoglu A, Sivertsson A, von Feilitzen K, Forsberg M, Zwahlen M, Olsson I, Navani S, Huss M, Nielsen J, Ponten F, Uhlen M: Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteomics 2014;13:397-406
57. Sun G, French CR, Martin GR, Younghusband B, Green RC, Xie YG, Mathews M, Barron JR, Fitzpatrick DG, Gulliver W, Zhang H: Comparison of multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for assessment of percentage body fat in a large, healthy population. The American journal of clinical nutrition 2005;81:74-78
58. Borga M, West J, Bell JD, Harvey NC, Romu T, Heymsfield SB, Dahlqvist Leinhard O: Advanced body composition assessment: from body mass index to body composition profiling. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 2018;66:1-9
59. Ntuk UE, Gill JM, Mackay DF, Sattar N, Pell JP: Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK biobank participants. Diabetes Care 2014;37:2500-2507
60. Huang-Doran I, Sleigh A, Rochford JJ, O'Rahilly S, Savage DB: Lipodystrophy: metabolic insights from a rare disorder. J Endocrinol 2010;207:245-255
61. Shulman GI: Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014;371:1131-1141
62. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R: Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011;54:2506-2514